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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/733,229	12/12/2003	Sui Xiong Cai	1735.0810001/RWE/RAS	4611

26111 7590 07/15/2005

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EXAMINER

AULAKH, CHARANJIT

ART UNIT PAPER NUMBER

1625

DATE MAILED: 07/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/733,229

Applicant(s)

CAI ET AL.

Examiner

Charanjit S. Aulakh

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-68 is/are pending in the application.
- 4a) Of the above claim(s) 4, 12, 23-26, 50, 57, 63, 66 and 67 is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 5-11, 13-22, 27-49, 51-56, 58-62, 64, 65 and 68 is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. ____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 3.
- 4) ☒ Interview Summary (PTO-413)
Paper No(s)/Mail Date. 06/20/2005.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: ____.

DETAILED ACTION

1. Claims 1-68 are pending in the application.

Election/Restrictions

2. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-3, 5-11, 13-22, 27-49, 51-56, 58-62, 64, 65 and 68, drawn to

Compounds of formula (I) where Q represents C and R1-R8 do not represent fused aryl or heteroaryl group, pharmaceutical compositions containing these compounds and a method of using these compounds, classified in class 546, subclass 94.

II. Claims 1, 2, 4-8, 10, 12-16, 18, 20-22, 27-48, 50-55, 57-61, 63-65 and 68, drawn to Compounds of formula (I) where Q represents N and R1-R8 do not represent fused aryl or heteroaryl group, pharmaceutical compositions containing these compounds and a method of using these compounds, classified in class 544, subclass 344.

III. Claims 1-8, 10-16 and 18-68, drawn to Compounds of formula (I) where Q represents C or N and R1-R8 do represent fused aryl or heteroaryl group, pharmaceutical compositions containing these compounds and a method of using these compounds, classified in class 546, subclass 70.

3. The inventions I, II and III as defined above are patentably distinct, each from the other since they are structurally so divergent that a reference showing compounds of invention I would not render compounds of inventions II or III prima facie obvious.

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Search required for e.g ; compounds of invention I in class 546, subclass 94 is not the same search required for e.g ; compounds of invention II in class 544, subclass 344 and therefore constitutes a burdensome search.

4. During a telephone conversation with the applicant's attorney, Mr. Robert A.

Schwartzman on June 20, 2005, a provisional election was made with traverse to prosecute the invention of group I, claims 1-3, 5-11, 13-22, 27-49, 51-56, 58-62, 64, 65 and 68. Affirmation of this election must be made by applicant in replying to this Office action. Claims 4, 12, 23-26, 50, 57, 63, 66 and 67 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

5. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-3, 5-11, 13-22, 27-42, 45 and 46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating breast cancer using instant compounds of formula (I) or pharmaceutically acceptable salts alone ,

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does not reasonably provide enablement for treating or ameliorating any cancer or disorder responsive to the induction of apoptosis, treating breast cancer using all possible prodrugs of compounds of formula (I) or using combination of instant compounds of formula (I) with other drugs. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The following eight different factors (see *Ex parte Foreman*, 230 USPQ at 547; *Wands, In re*, 858.F. 2d 731, 8 USPQ 2d 1400, Fed. Cir. 1988) must be considered in order for the specification to be enabling for what is being claimed:

Quantity of experimentation necessary, the amount of direction or guidance provided, presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability and the breadth of claims. In the instant case, the specification is not enabling based on at least four of the above mentioned eight different factors such as quantity of experimentation necessary, the amount of direction or guidance provided, the state of the prior art, presence of working examples, unpredictability and the breadth of claims.

The instant specification teaches (see page 2, second paragraph) that mammalian apoptosis system appears to involve a cascade of caspases, or a system that behaves like a cascade of caspases. At present, the caspase family of cysteine proteases comprises 14 different members, and more may be discovered in the future. The applicants provide some data on Caspase activity in table 1 on page 74 and also show inhibitory effect on cell proliferation using breast cancer cell lines (see table II). In

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regard to Caspase activity, first of all, it is not clear from the data which one member of already known 14 different members of Caspase family of cysteine proteases was used in this study. Secondly, there is lot of unpredictability even using this one member since there is huge variation in EC50 values among 13 compounds tested (see data in table I). There is no teaching either in the specification or prior art showing involvement of this specific cysteine protease in induction of apoptosis in every known cancer or disorder in the art. There are no working examples present showing efficacy of instant compounds alone, their prodrugs, or combination of instant compounds with any other drug in known animal models of every known disorder responsive to apoptosis or all known cancer cell lines. There is no direction or guidance present in the specification how the instant compounds having activating effect on only one member of Cascade family or having inhibitory effect on cell proliferation using only breast cancer cell line in vitro will be able to treat and/or ameliorate every possible known disorder responsive to induction of apoptosis by all 14 different members of cysteine proteases. The instant compounds of formula (I) encompasses several hundreds of thousands of compounds based on the values of variables R1-R8, Ar and L and therefore, in absence of such teachings, guidance, presence of working examples and unpredictability, it would require undue experimentation to demonstrate the efficacy of instant compounds in known animal models of every known disorder responsive to induction of apoptosis by all 14 different members of cysteine proteases and hence their utility in treating these disorders.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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9. Claims 1-3, 5-11, 13-22, 27-49, 51-56, 58-62, 64, 65 and 68 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1-3, 5-11, 13-22, 27-49, 51-56, 58-62, 64, 65 and 68, the term ---prodrug--- is indefinite since specific prodrugs and methods of preparing them are not defined.

In claims 1, 27, 30, specific disorders or cancers responsive to induction of apoptosis are not defined. Also, the term --ameliorating--- is indefinite since the degree of amelioration (20%, 40%, 60%, 80% or 100%) is not defined and furthermore, it is not clear how this amelioration is assessed in vivo following administration of instant compounds of formula (I).

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

10. Claims 47-49, 52-56, 59-62 and 65 are rejected under 35 U.S.C. 102(b) as being anticipated by Henrick (Aust. J. Chem., cited on applicants form 1449).

Henrick discloses Pyridinium Ylides in synthesis. The compound (XI) disclosed (see page 2470) by Henrick anticipates the instant claims when L is $-C=O$ and both R1 and R2 represent alkylcarboxylate in the instant compounds of formula (I).

11. Claims 47-49, 52-56, 59-62 and 65 are rejected under 35 U.S.C. 102(b) as being anticipated by Irwin (J.C.S. Perkins I, cited on applicants form 1449).

Irwin discloses Pyrrolo[1,2-a]quinolines. The compound (7) disclosed (see page 250) by Irwin anticipates the instant claims when L is $-C=O$, R1 represents alkyl and R2 represents alkylcarboxylate in the instant compounds of formula (I).

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12. Claims 47-49, 52-56, 59-62 and 65 are rejected under 35 U.S.C. 102(b) as being anticipated by Kuo (J. Heterocyc. Chem., cited on applicants form 1449).

Kuo discloses Synthesis and reactions of 2,7-dimethylpyrrolo[1,2-a]quinoline. The compound V disclosed (see page 393)) by Kuo anticipates the instant claims when L is -C=O and both R1 and R6 represent alkyl in the instant compounds of formula (I).

13. Claims 47-49, 52-56, 59-62 and 65 are rejected under 35 U.S.C. 102(b) as being anticipated by Tewari (J. Chem. Eng. Data, 1982).

Tewari discloses studies on 1,3-dipolar cycloaddition reactions of some cycloimmonium Ylides. The compounds 7a-7c and 9a-9g (see table 1 on page 101) disclosed by Tewari anticipate the instant claims when L is -C=O , R1 represents H or alkylcarboxylate and R2 represents alkylcarboxylate in the instant compounds of formula (I).

14. Claims 47-49, 52-56, 59-62 and 65 are rejected under 35 U.S.C. 102(b) as being anticipated by Tewari (J. Chem. Eng. Data, 1983).

Tewari discloses studies on 1,3-dipolar cycloaddition reactions of some cycloimmonium Ylides. The compounds 7a-7d and 9a-9h (see table 1 on page 284) disclosed by Tewari anticipate the instant claims when L is -C=O and both R1 and R2 represent alkylcarboxylate in the instant compounds of formula (I).

15. Claims 47-49, 52, 54-56 and 59 are rejected under 35 U.S.C. 102(b) as being anticipated by Georgescu (Revue Roumaine de Chimie).

Georgescu discloses N-bridged heterocyclic compounds. The compounds 8a-8d (see table 2 on page 358 and scheme 2 on page 359) disclosed by Georgescu anticipate

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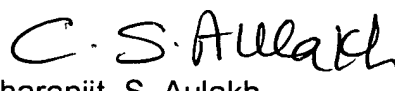
the instant claims when L represents $-C=O$ and Ar represents heteroaryl group in the instant compounds of formula (I).

16. Claims 1-3, 5-8, 10, 11, 13-16, 18-22, 27-49, 51-56, 58-62, 64, 65 and 68 are objected for containing non-elected subject matter.

17. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charanjit S. Aulakh whose telephone number is (571)272-0678. The examiner can normally be reached on Monday through Friday, 8:30 A.M. to 5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on (571)272-0562. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Charanjit S. Aulakh
Primary Examiner
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